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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/552,314	09/05/2006	Annie Bardat	0040-0158PUS1	1865

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EXAMINER	
KIM, YUNSOO	
ART UNIT	**PAPER NUMBER**
1644	

NOTIFICATION DATE	DELIVERY MODE
04/14/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/552,314	BARDAT ET AL.	
	Examiner	Art Unit	
	YUNSOO KIM	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-5 and 7-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2-5 and 7-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/12/10 has been entered.

2. Claims 2-5 and 7-11 are pending and are under consideration upon entry of the response filed on 12/14/09.

3. In light of Applicants' amendment filed on12/14/09, the objection and the rejections set forth in the office action mailed on 7/14/09 (see sections 3 and 5-8) have been withdrawn.

4. Claims 2-5 and 7-11 are objected to because of the following informalities: Claims 2, 7-11 recite "immunoglobulin**s** G composition" or "immunoglobulin**s** G compositions", respectively. The immunoglobulin G is an antibody molecule having 2 heavy chains and 2 light chains. Even though it has a tetrameric structure, it is should be in a singular form as it consists of only one isotype (G). Further, the term "dimmers" in claim 11 is noted. Appropriate correction is required.

5. The following rejections remain.
Note the changes of claim numbers upon entry of the amendment filed on 12/14/09.

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 2, 3, 5, 7, 9, and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by U. S. Pat. No. 5,945,098 (IDS reference, of record) as is evidenced by the MSDS for glycine, of record, for the reasons set forth in the office action mailed on 7/14/09.

Upon cancellation of claim 1, Applicant has amended the dependency of claims 3-5 and 7-11. Note the currently amended claims 3 and 5 are identical to the previously rejected claims 15 and 17 (currently canceled) and have been added to this rejection. Further, claims 7, 9, and 11 are included in this rejection upon change of the dependency.

Claim 2 recites "consisting essentially of" and the transitional phrase is considered open to include other components in addition to the recited sugar alcohol, glycine and non-ionic detergent.

The '098 patent teaches an aqueous IgG formulation comprising mannitol, glycine and non-ionic detergents such as Tween 20 (claims 1-12, examples 1-15) and the formulation is stable.

Note that the intended use of the claimed formulation consisting essentially of a sugar alcohol, glycine and a non-ionic detergent is to stabilize IgG in liquid form or in lyophilized form. Given that the claimed formulation and the prior art formulation do not result in a structural difference, the prior art formulation is capable of performing the intended use and it meets the limitations of claim 2.

Given that the prior art formulation and the claimed formulation both comprise sugar alcohol, glycine and a non-ionic detergent, having the polymer contents measured after the storage conditions recited in claims 9 and 11 are inherent properties of the

formulation comprising sugar alcohol, glycine and a non-ionic detergent. Therefore, the limitations of claims 9 and 11 have been met.

The '098 patent further teaches that the concentration of glycine is about 0.1-0.3M, (example 1, col. 5, lines 13-18, claim 1) and that the concentration of polysorbate is 0.002-0.004% (example 1). Given that the molecular weight of glycine is 75.07 as is evidenced by the MSDS for glycine, "about 0.1M-0.3M" is equivalent to 7g/l to 21g/l, and thus claim 3 is included. Therefore, the reference teachings anticipate the claimed invention.

Applicant's arguments filed on 12/14/09 have been fully considered but they were not persuasive.

Applicant has asserted that the transitional phrase "consisting essentially of" should be interpreted to define the composition contains the recited material and potentially other components that do not materially affect the basic and novel characteristics of the invention. Based on this, Applicant has asserted that the '098 patent does not teach all the limitations of the claimed invention. Applicant has further asserted that the specification of the instant application discloses that glucose, fructose, and/or polyethylene glycol (PEG) should be avoided as they provoke the onset of Maillard reactions (see pages 6-7 of the response). Applicant has asserted that the '098 patent does not disclose any formulation does not contain PEG and the '098 patent fails to teach all the limitations of the claimed invention.

However, the specification of the instant application does not clearly define what is encompassed by the stabilizers which do not affect the characteristics as Applicant has asserted.

The specification states under "Detailed description of the preferred embodiment" (p.5):

The stabilising formulation according to the invention can include, beside a sugar alcohol, glycine and a non-ionic detergent, at least one other additive. This additive can

be a compound selected from the different categories of stabilizers classically used in the technical field of the invention, such as surface active agent, sugars, and amino acids, and as well as excipient added to the formulation in order to adjust, for example, the pH, the ionic strength, etc.

Rather, very broad range of additives are encompassed by the stabilizers and the instant specification does not specifically exclude addition of PEG. As is taught by the '098 patent, PEG is used as a stabilizer, and it is "classically used in the technical field" in the immunoglobulin art. Note that the claim does not exclude addition of PEG, either.

Applicant has asserted that the PEG should be avoided during the lyophilization at acidic pH. However, such condition is not claimed. Even though some stabilizers that may provoke onset of Maillard reactions, such reaction occurs upon lyophilization. Note that the formulation in claim 2 does not have to undergo lyophilization and the prior art formulation is aqueous. Note that the claims reciting "lyophilized" form (e.g. claims 8 and 10) are not included in this rejection. Applicant argues the limitations that are not claimed.

Further, Applicant has asserted that glucose or fructose is avoided in individual suffering from renal failure and/or diabetes. However, this characterization is based on the population group in the specific therapy and this characterization is not related to basic and novel characteristics of the claimed invention. Note that the claimed invention relates to stabilizing IgG.

As discussed above, the specification of the instant application does not define stabilizers that do or do not affect the basic and novel characteristics of the claimed invention, the phrase "consisting essentially of" is considered open and the '098 patent is a proper anticipatory reference. See MPEP 2111.03

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office Action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 2-5 and 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable U.S. Pat. No. 4,597,966, of record, in view of EP 0392,717A1, of record, and U.S. Pub. No. 2006/0246060A1, of record, as is evidenced by MSDS for mannitol and glycine, of record, for the reasons set forth in the office action mailed on 7/14/09.

The '966 patent teaches a stabilizing IgG formulation comprising IgG, histidine and glycine at concentration of about 0.1M (claims 1-15).

The disclosure of the '966 patent differs from the instant claimed invention in that it does not teach the addition of sugar alcohol (e.g. mannitol) at concentration between 30g/l-50g/l and a non-ionic detergent currently recited in claim 4 and where the immunoglobulin is lyophilized as in claims 8 and 10 of the instant application.

The '717 publication teaches that addition of mannitol and glycine at 1:1 ratio improves stability of antibody and inhibits aggregation (claims 1-10, example 1). The '717 publication further teaches the lyophilization is known to improve storage time of the

antibody and the addition of mannitol/glycine solves the potential aggregation problems that may arise during the lyophilization (p.2). The '717 publication teaches the lyophilized antibody formulation comprising mannitol/glycine (claim 8-9).

As is evidenced by MSDS of mannitol and glycine, the molecular weights for mannitol and glycine are 182 and 75, respectively. The recited concentration ranges of mannitol in claim 4 and the concentration ranges of glycine in claim 5 are equivalent to 160mM-275mM and 100mM-150mM, respectively. Further, given that the term "about" is flexible and includes the concentration near 0.1M, the concentration of glycine in the '966 patent "about 0.1M" (e.g. claim14) reads on the claimed 7-10g/l of glycine. Based on the glycine concentration, the mannitol concentration in light of the '717 publication is "about 0.1M" and reads on the claimed concentration of 30g/l of claim 4 of the instant application. Therefore, claims 4 and 5 are included in this rejection.

The '660 publication teaches addition of 0.005% of non-ionic detergent (e.g. polysorbate 20) improves stability by reducing aggregation ([0021]).

Applicant is deemed to define "consisting essentially of" excludes PEG. Note that none of the references above discloses addition of PEG and it is considered the prior art formulation is prepared without PEG, and no process is required to remove PEG.

Further claims 9-11 are included in this rejection because the combination of references results in the claimed formulation and having polymers less than 0.3% after 12 m at room temperature, or includes dimers less than 7% after 24m at 4°C as recited in claims 9-11 are expected properties of the IgG formulation comprising mannitol, glycine and non-ionic surfactant at 0.005%.

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to add mannitol at the concentration as taught by the '717

publication and non-ionic detergent the '660 publication to the antibody formulation as taught by the '966 patent.

One of ordinary skill in the art at the time the invention was made would have been motivated to do so because the addition of mannitol and glycine improves stability of protein upon storage and delivery by reducing aggregation and the lyophilization improves overall storage time of the antibody formulation.

Therefore, it is prima facie obvious to combine two compositions each of which is taught by prior art to be useful for same purpose in order to form third composition that is to be used for very same purpose; idea of combining them flows logically from their having been individually taught in prior art. In re Kerkhoven, 205 USPQ 1069, CCPA 1980. See MPEP 2144.06

From the teachings of the references, it would have been obvious to one of ordinary skill in the art to combine teachings of the references and there would have been a reasonable expectation to success in producing the claimed invention. Therefore, the invention as a whole was a prima facie obvious to one of ordinary skill in the art at the time the invention was made as evidenced by the references, especially in the absence of evidence to the contrary.

Applicant's arguments filed on 12/14/09 have been fully considered but they were not persuasive.

Applicant has asserted that the combination of the references is not obvious and because the combination of the reference does not result in the claimed invention.

Applicant has further argued that the PEG is not suitable for lyophilization since PEG induces precipitation based on the teachings of the '098 patent. Applicant has asserted that none of the references teaches the removal of PEG.

Applicant has further asserted that the '966 patent does not teach further addition of other additives, and 'the 717 publication concerns immunogloulin conjugates resulting from the vinca hydrazine. Moreover, Applicant has asserted that the combined formulation is not expected to achieve polymer contents as recited in claims 9-11 of the claimed invention (Table 1 of the '717 publication). Further, Applicant has asserted that the '060 publication avoids addition of the non-ionic surfactants in lyophilized formulation. Applicant has asserted that the combination of the references would inevitably comprise histidine, glycine, mannitol and sucrose and there is no reasonable expectation of success to prepare the claimed stabilizing formulation.

However, the primary reference for this rejection is the U.S. Pat. No. 4,597,966 and none of the cited references disclose PEG. As Applicant is deemed to define "consisting essentially of" excludes PEG, the rejection is made based on the U.S. Pat. No. 4,597,966. Note that none of the references above discloses addition of PEG and it is considered the prior art formulation is prepared without PEG, and no process is required to remove PEG. Therefore, Applicant's assertion based on that the '098 patent is not relevant to this rejection.

Further, Applicant's assertion of the '966 patent does not require other excipients in addition to histidine and glycine is misleading. The '966 patent discloses addition of sodium chloride, cysteine, and/or maltose for further characterization (tables I-II, col. 9-10). Further, the claims of the '966 patent uses "comprising" and this term is considered open and allows addition of other unrecited components.

Moreover, Applicant uses the table 1 of the '717 publication as a basis for the prior art formulation does not achieve the polymer content less than 0.3% as required by the claims 9-11 of the instant application. Applicant interprets 12.6% of table 1 (note percent aggregates) as % polymer content. However, note that the claimed formulation is required to have sugar alcohol, glycine and a non-ionic detergent while the example 2

(table 1) of the '717 publication is based on mannitol (e.g. sugar alcohol) and glycine. Therefore, the formulation of the '717 publication only serves an intermediate composition (meant to differentiate from the claimed composition) compared to the claimed composition comprising all 3 requirements. Moreover, the art recognizes that the contexts of "aggregates" and "% dimmer or % polymer content" are different. As seen in the table 1 of the '966 patent, % dimer content is defined differently from % aggregate. Therefore, the "% aggregate" as described in the '717 publication cannot be an accurate measurement for "percent dimer content" as recited in the claim 9-11 of the instant application.

Regardless, table 1 of the '717 publication shows significant reduction of aggregate formation upon addition of mannitol to the glycine alone. Note that addition of mannitol/glycine reduces the aggregates from ~26% to ~13%. This provides reasonable expectation of success and motivation to add mannitol in addition to glycine. Moreover, the '717 publication does not limit the immunoglobulin sources from conjugates of vinca hydrazine but any immunogloulins from any sources (p.4)

Obviousness does not require absolute predictability but only reasonable expectation of success. See MPEP 2143.02.

In addition to the combination of glycine and mannitol, the '060 publication adds motivation to add non-ionic surfactant and clearly states that aggregation is reduces and minimizes the particle formation ([021]) and stabilizing surfactant is added upon frozen or lyophilized condition ([0006]).

Applicant's assertion of the combined formulation would inevitably comprise histidine, glycine, mannitol and sucrose is erred. As discussed above, the '966 patent teaches antibody formulation comprising glycine, the '717 publication teaches motivation to combine mannitol to glycine and stabilization during lyophilization and the '060

publication teaches addition of non-ionic surfactant. The combination of the references does not have to combine all the components of references as Applicant has asserted.

One cannot show nonobviousness by attacking references individually where the rejections are based on combination of references. See MPEP 2145.

10. No claims are allowable.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to YUNSOO KIM whose telephone number is (571)272-3176. The examiner can normally be reached on M-F, 9-5. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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April 9, 2010

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